

RESEARCH ARTICLE

Effect of Maternal Familial Mediterranean Fever on Fetal Pulmonary Artery Acceleration/Ejection Time

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Abstract

Introduction: Autoinflammation and increase in free oxygen radicals due to maternal familial mediterranean fever (FMF) may affect fetal lung maturation and cause changes in fetal pulmonary artery Doppler parameters. We aimed to investigate the fetal pulmonary artery acceleration time/ejection time (PATET) ratio in the pregnancies complicated with familial mediterranean fever (FMF).

Methods: This cross-sectional study included 32 pregnant women with FMF, and 64 gestational ages matched healthy pregnant women, between the 29-30 gestational weeks. Maternal characteristics and fetal ultrasonographic information were recorded. Fetal pulmonary artery acceleration time (AT) and ejection time (ET) were measured manually and PATET ratio were calculated in the study groups. The duration of the disease and the AT and PATET measurements were analyzed with the Pearson correlation test.

Results: The study groups were similar in terms of maternal characteristics, gravidity, parity and gestational week at the time of examination. AT and ET values were found to be significantly shorter and PATET (AT/ET) was found to be significantly lower in pregnant women complicated with FMF. A moderately significant negative correlation was found between the time elapsed since FMF diagnosis and fetal pulmonary artery acceleration time. ($r=-.566$, $p=.001$) and PATET ($r=-.533$, $p=.002$)

Conclusion: This is the first study to investigate the fetal pulmonary artery Doppler indices in the pregnancies with FMF. In the presented study, it was shown that FMF significantly shortened the fetal pulmonary acceleration and ejection time and significantly reduced the PATET ratio. In addition, as the time elapsed from the diagnosis of the disease increased, it was shown that the shortening in AT and the decrease in PATET were higher, with a significant moderate negative correlation between the duration of the disease and these values.

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Introduction

Familial Mediterranean Fever (FMF) is a chronic inflammatory disease manifested by recurrent attacks of fever, neutrophil induced painful serosal inflammations such as peritonitis, pericarditis, synovitis and amyloid deposition in the kidneys.¹ FMF with autosomal recessive inheritance is more common in certain populations such as Jewish, Armenian, Arab and Turkish. FMF occurs in recurrent and self-limiting episodes, with the first attack usually in childhood or early adolescence. The diagnosis of FMF is made under the age of five in approximately 60% of the patients and under the age of 20 in 90% of them.² It is caused by impaired pyrin protein function due to mutations in the MEFV gene on chromosome 16³. Disruption of this protein, which is mostly expressed in neutrophils, causes an increase in interleukin 1(IL1) and reactive oxygen species secretions and excessive inflammatory response of body itself.⁴ The main cause of organ and tissue damage in FMF is free oxygen radicals with increased secretion from neutrophils. Subclinical inflammation, which continues in silent periods between acute attacks, may cause Amyloid-A accumulation called amyloidosis in kidney, liver and cardiac tissues.⁵ Colchicine is the treatment option that effectively prevents acute attacks and amyloidosis triggered by subclinical inflammation that continues between attacks in FMF.

Acute attacks in maternal FMF can complicate pregnancy and cause obstetric and perinatal problems. Peritonitis during acute attacks has been associated with an increased rate of preterm birth, premature rupture of membranes and cesarean section in FMF pregnancies.⁶ In addition, complications such as fibrosis and amyloidosis, which develop due to autoinflammation in FMF, may lead to mechanical obstruction in the tuba uterine and difficulty in obtaining pregnancy. By disrupting sperm and oocyte proliferation and preventing implantation, the rate of recurrent pregnancy loss also increased in pregnancies with FMF.⁷ Colchicine can also be used safely during pregnancy, significantly reducing recurrent pregnancy loss and obstetric complications caused by acute attacks during pregnancy.⁸

Fetal lung development may be interrupted and delayed by prematurity and many other maternal or obstetric complications. Free oxygen radicals, which also form the basis of the pathophysiology of FMF, may cause damage to the pulmonary epithelium and surfactant inactivation, thus disrupting fetal

lung maturation.⁹⁻¹¹ Fetal lungs, which are the last to complete their development, begin to form in the embryonic period and continue to develop throughout pregnancy and even up to 8 years of age. As the fetal lungs mature, pulmonary blood flow increases while the resistance in the pulmonary vessels decreases in the later weeks of gestation^{12,13} Therefore, fetal pulmonary artery Doppler examination gives information about fetal lung maturation.

There are many studies investigating whether fetal pulmonary artery Doppler may predict neonatal respiratory distress syndrome (RDS).¹⁴⁻¹⁷ Many tests have been developed to detect lung maturity, but although they have been used in clinical practice for many years, most of these are time-consuming, expensive, and invasive tests. Pulmonary acceleration time/ejection time (PATET), an alternative method to invasive techniques, is a pulmonary artery Doppler parameter that can show fetal lung maturation non-invasively.^{16,18-20}

We hypothesized that autoinflammation and increase in free oxygen radicals due to FMF may affect fetal lung maturation and cause changes in fetal pulmonary artery Doppler parameters. In the presented study, we aimed to compare fetal pulmonary artery acceleration/ejection time (PATET) in pregnancies with FMF and in healthy pregnancies.

Material and Methods

The study in Cross Sectional design was carried out between July 2022 and January 2023 in the maternal-fetal department. The study was started after ethics committee approval from Medical Research Ethical Department of Ankara City Hospital (E2-22-2141). All participants were informed and written consent was obtained.

Thirty-two pregnant women with FMF at 29-30 weeks of gestation and 64 randomly selected healthy pregnant women whose gestational week and maternal characteristics were matched with the study group were included in our study. Pregnant women with fetal anomaly, fetal growth restriction, preterm rupture of membranes, multiple pregnancy, and all maternal diseases except FMF were excluded from the study. Maternal characteristics, gestational week at which ultrasonography was performed, duration of FMF disease, drug use information, and the number of attacks during pregnancy were recorded according to the informa-

tion obtained from the patient and hospital records. Betamethasone treatment was administered after ultrasonographic examination in required patients.

The patients included in the study were evaluated at 29 and 30 weeks of gestation and all the ultrasonographic examinations were performed by a single perinatology fellow with experience in fetal ultrasound by using the 3-5 MHz convex ultrasound transducer of Voluson E8 (GE Healthcare, Milwaukee, WI). After routine fetal biometric measurements and fetal well-being were evaluated, the right ventricular outflow tract, pulmonary valves and pulmonary artery bifurcation were visualized in the short axis view of the heart, in which there was no fetal respiration and movement. By keeping the insonation angle below 15 degrees, and setting the sample interval to 3 mm, the Doppler precursor was placed between the pulmonary valves and the bifurcation of the main pulmonary artery, and minimum three optimal cardiac cycle waveforms were obtained. Acceleration time (AT), defined as the time from onset of ventricular systole to the peak flow rate and ejection time (ET), defined as the time from onset of the ventricular systole to the end, were measured manually and PATET (AT/ET) was calculated (Figure 1). Measurements were obtained in three separate waveforms and the average was recorded.

Statistical Analysis

The sample size was analyzed by using the G Power software ((version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany) 21. A sample size of 32 patients in the case group and 64 control was calculated with an effect size of 0.80 and p-value of 0.05 (two-tailed) and a power of 95%. Statistical analyses were performed using Social Sciences (SPSS), software version 17.0 (SPSS Inc, Chicago, IL). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median (IQRs (Interquartile Ranges)) values for numerical data that do not follow a normal distribution. For comparing the values of two independent groups, the "Independent t-test" for normal distribution variables and the "Mann-Whitney U test" for non-normal distribution variables were used. Distribution of the AT, ET and PATET measurement between the groups was shown with the error bar. Error bars indicate the mean and 95% confidence interval of AT, ET and PATET in study groups (Figure 2a, 2b and 2c). The duration of the disease and the AT and PATET measurements were analyzed with the Pearson correlation test and were shown with Scatter Plot (Figure 3a and 3b). In all analyses, an alfa level of 0.05 was considered significant.

Results

Thirty-two pregnant women with FMF were included in the study group and 64 healthy pregnant women were included in the control group. The study groups were similar in terms of maternal age, pre-pregnancy body mass index (BMI), gravidity, parity and gestational week at the time of examination. (Table 1).

AT and ET values were found to be significantly shorter and PATET (AT/ET) was found to be significantly lower in pregnant women complicated with FMF (Table 1). The distributions of AT, ET, and PATET measurements were also shown with error bars (Figure 2a, 2b, and 2c). Error bars indicate the mean and 95% confidence interval of AT, ET and PATET in the study groups. The mean duration of disease diagnosis was 9.8 years. The number of patients with FMF who had an attack during pregnancy was 4 (12.5%). There was no patient who had more than one attack during

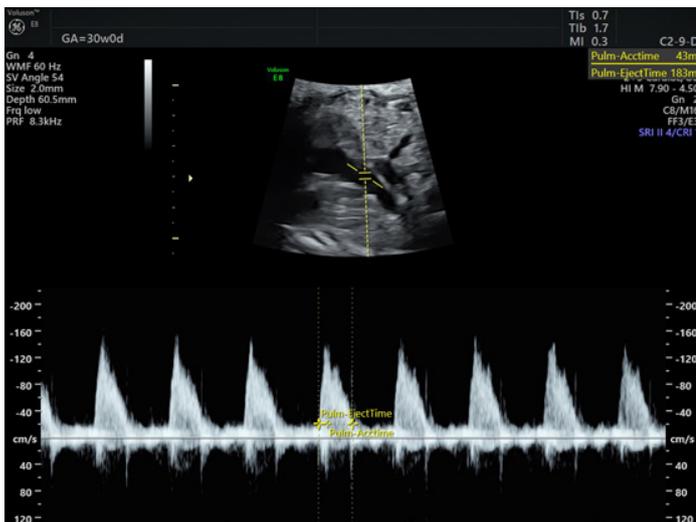


Figure 1: Measurement of the acceleration time and ejection time of the fetal pulmonary artery with spectral Doppler ultrasound

pregnancy. Twenty-six pregnancies with FMF were using hydroxychloroquine. There was no one using corticosteroid therapy in patients who had an attack.

A moderately significant negative correlation was found between the time elapsed since FMF diagnosis and fetal pulmonary artery acceleration time. ($r=-.566$, $p=.001$) and PATET ($r=-.533$, $p=.002$) (Figure 3a and 3b).

Table 1: Comparison of fetal pulmonary artery Doppler indices of the all participants

	FMF (n=32)	Control group (n=64)	p value
Age (years)	31.1±5.6	30.5±4.2	.574*
Gravidity	2 (1-3)	1 (1-2)	.231†
Parity	0 (0-1)	0 (0-1)	.129†
Abort	1 (0-2)	0 (0-1)	.153†
Pre-pregnancy BMI (kg/m ²)	24.9±3.4	25.5±2.7	.307*
Gestational age at examination (Weeks)	30 (29-30)	30 (29-30)	.775†
Acceleration time (AT) (ms)	34.7±2.6	38.8±2.4	<.001*
Ejection time (ET) (ms)	189.8±11	195.2±10.1	.019*
AT/ET ratio	0.18±0.02	0.20±0.01	<.001*

Values are presented as mean± standard deviation

* Independent t-test

† Mann Whitney U test

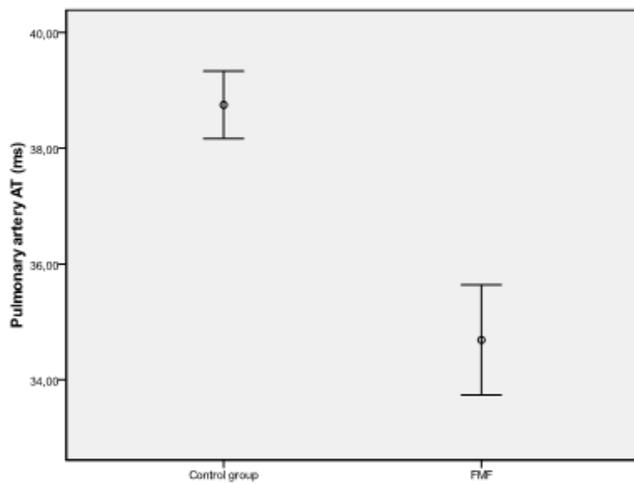


Figure 2a: Comparison of fetal pulmonary artery AT in pregnant women with FMF and control group with error bar

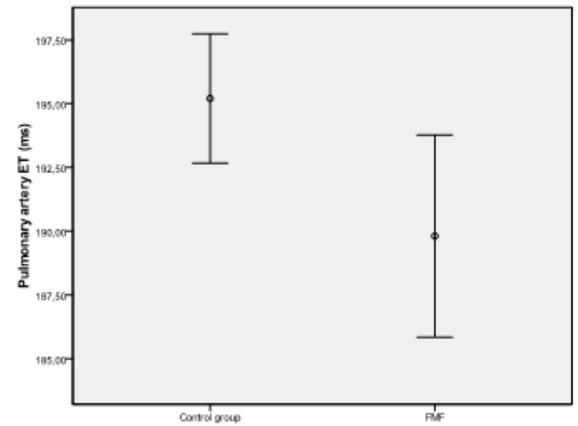


Figure 2b: Comparison of fetal pulmonary artery ET in pregnant women with FMF and control group with error bar

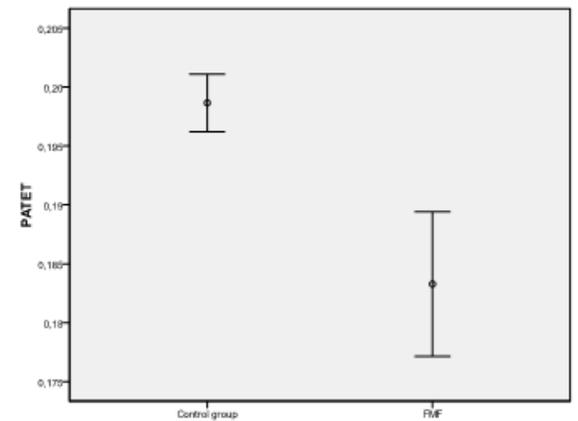


Figure 2c: Comparison of fetal pulmonary artery PATET in pregnant women with FMF and control group with error bar

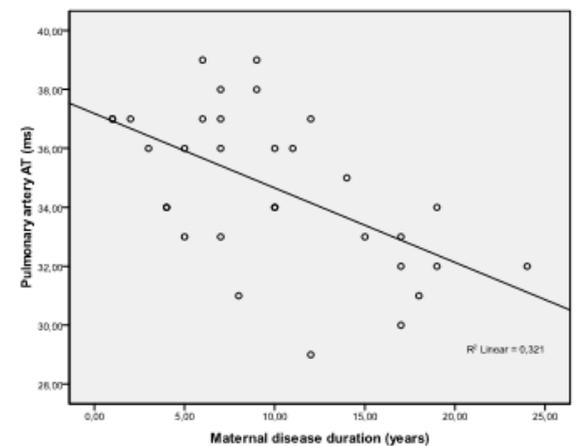


Figure 3a: Scatter plot demonstrating the correlation between maternal disease duration (years) and fetal pulmonary artery acceleration time (ms)

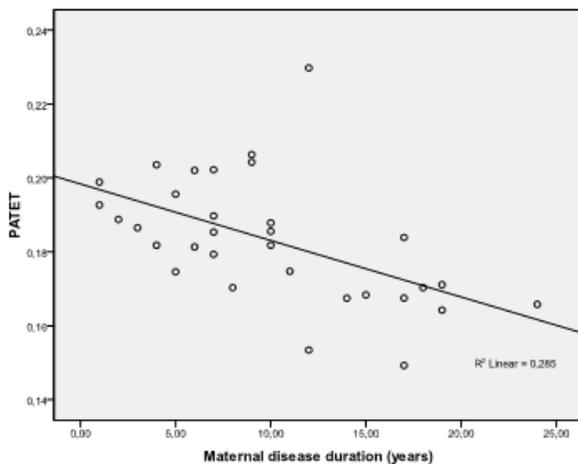


Figure 3b: Scatter plot demonstrating the correlation between maternal disease duration (years) and fetal pulmonary artery AT/ET ratio

Discussion

FMF is a regional and rare disease encountered in certain populations. The effect of FMF on pregnancy and perinatal outcomes has been investigated in many studies 6,7. However, this is the first study to investigate whether FMF affects fetal pulmonary circulation and hence lung maturation. In the presented study, it was shown that FMF significantly shortened the fetal pulmonary acceleration and ejection time and significantly reduced the PATET ratio. In addition, as the time elapsed from the diagnosis of the disease increased, it was shown that the shortening in AT and the decrease in PATET were higher, with a significant moderate negative correlation between the duration of the disease and these values.

Chaoui et al showed that blood flow and resistance in the fetal pulmonary circulation have been shown to change as pregnancy progresses and with fetal lung maturation in the previous studies 22. With the maturation of the fetal lungs, reduction in pulmonary arterial pressure and increase in blood flow have been demonstrated by the use of conventional Doppler and has become an alternative method to invasive tests used to determine lung maturation 12,13. It has been shown that the AT/ET ratio increases as the gestational week progresses, and it has been suggested that this was due to fetal lung maturation and a decrease in pulmonary artery resistance, thus prolonging the acceleration time. 22. The relationship between pulmonary

artery Doppler indices and amniotic fluid markers showing fetal lung maturation was investigated, and an inverse correlation only between the PATET ratio and the lecithin/sphingomyelin ratio in amniotic fluid was found. No significant correlation was found with other indices of fetal pulmonary artery Doppler and fetal lecithin/sphingomyelin ratio 14.

It is known that maternal chronic autoimmune diseases that cause subclinical inflammation in the placenta are associated with an increased risk of fetal growth retardation and early and late intrauterine death 23. Mononuclear infiltration due to autoimmune diseases may cause placental villitis, chronic chorioamnionitis and/or chronic deciduitis. Intense inflammation and free oxygen radicals in the placenta may cause damage to fetal membranes and apoptosis in trophoblasts, which may be associated with poor perinatal outcomes such as unexplained bleeding during pregnancy, fetal growth restriction and fetal death 24.

Cytokines and free oxygen radicals due to maternal infection and inflammation may affect fetal pulmonary circulation. In a recent study investigating the effects of autoimmune diseases such as maternal systemic lupus erythematosus, Sjögren's syndrome and antiphospholipid antibody syndrome on the fetal pulmonary circulation, it was shown that inflammation significantly reduces the ratio of AT and AT/ET in the fetal pulmonary artery 25. Fetal pulmonary artery AT and PATET rates were significantly lower in COVID-19 recovered pregnancies 26. In the study examining the prediction of neonatal RDS of fetal pulmonary artery Doppler parameters in pregnancies infected with COVID-19, fetal pulmonary artery AT and PATET ratio were found to be significantly lower in newborns admitted to the neonatal intensive care unit (NICU) due to RDS 27. In the presented study, although the shortening in AT was more pronounced, we also observed a significant shortening in ET. The shorter AT in the FMF group was due to the high resistance in the fetal pulmonary vessels, high pulmonary artery pressure, and delaying fetal lung maturation by the inflammation. We thought that the shortening in ET was due to the fact that the inflammation in FMF may cause change in systolic function in the fetal heart. It was also previously showed that maternal FMF can cause diastolic and systolic function changes in the fetal heart 28. The efficacy of fetal pulmonary artery PATET ratio was investigated to predict neonatal respiratory

complications in preterm prelabor rupture of membranes pregnancies, and it was found that PATET, when the gestational age (confounding factor) was adjusted, could not predict respiratory complications 19. On the contrary, in the study investigating the prediction of fetal pulmonary artery PATET value for neonatal RDS, a negative correlation was shown with low PATET value indicating an increase in neonatal RDS 18. The PATET ratio was found to be inversely proportional to the pulmonary artery pressure in the fetal and adult periods and low PATET values were found to reflect pulmonary hypertension 29. In this study conducted in adults, shortening of both AT and ET was observed as a result of the change of pulmonary valve movements in the presence of pulmonary hypertension, and the PATET rate was also found to be significantly lower in patients with pulmonary hypertension. The most important limitation of our study is that it was in a cross-sectional design, only one measurement was made in the pregnant women included in our study, they did not have repeated examinations, and the obtained data were not associated with perinatal and neonatal outcomes. Longitudinal studies in which ultrasonographic data are associated with perinatal outcomes, with larger populations of patients in a prospective design will provide more information on this issue.

Conclusion

This is the first study to investigate the effect of maternal FMF on fetal pulmonary artery Doppler. FMF may affect the fetal pulmonary artery blood flow with the inflammatory environment it creates and the excess free oxygen radicals secreted. It should be kept in mind that maternal FMF, which causes shorter fetal pulmonary artery AT and ET, and lower PATET rate, may disrupt in the maturation of the fetal pulmonary vascular bed, and hence increase fetal pulmonary morbidity and mortality. Fetal pulmonary artery Doppler evaluation is a noninvasive and easily applicable method that shows the maturation of the pulmonary vascular bed and fetal lung. Clinical use of fetal pulmonary artery Doppler with other Doppler modalities and biophysical profile may provide additional benefit in predicting perinatal outcomes and taking precautions.

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Conflicts of Interest

The authors have no conflicts of interest.

Funding Statement

None

References

1. Migita K, Fujita Y, Asano T, Sato S. The Expanding Spectrum of Autoinflammatory Diseases. *Internal medicine (Tokyo, Japan)*. 2023;62(1):43-50.
2. Çelen Yoldaş T, Özdel S, Karakaya J, Bülbül M. Developmental and Behavioral Problems of Preschool-Age Children with Chronic Rheumatic Diseases. *Journal of developmental and behavioral pediatrics : JDBP*. 2022;43(3):e162-e169.
3. Kışla Ekinci RM, Balcı S, Erol AH, Karagöz D, Ufuk Altıntaş D, Bisgin A. Differentiating children with familial Mediterranean fever from other recurrent fever syndromes: The utility of new Eurofever/PRINTO classification criteria. *Archives of rheumatology*. 2021;36(4):493-498.
4. Malik J, Shabbir A, Nazir A. Cardiovascular Sequelae and Genetics of Familial Mediterranean Fever: A Literature Review. *Pulse (Basel, Switzerland)*. 2021;8(3-4):78-85.
5. Bitik B, Hatipoğlu B, Sayın B, et al. Long-term results of kidney transplantation in patients with familial mediterranean fever. *Clinical transplantation*. 2022:e14888.
6. Yasar O, Iskender C, Kaymak O, Taflan Yaman S, Uygur D, Danisman N. Retrospective evaluation of pregnancy outcomes in women with familial Mediterranean fever. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2014;27(7):733-736.
7. Sotskiy PO, Sotskaya OL, Hayrapetyan HS, et al. Infertility Causes and Pregnancy Outcome in Patients With Familial Mediterranean Fever and Controls. *The Journal of rheumatology*. 2021;48(4):608-614.
8. Rabinovitch O, Zemer D, Kukia E, Sohar E, Mashiach S. Colchicine treatment in concep-

- tion and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. *American journal of reproductive immunology* (New York, N.Y. : 1989). 1992;28(3-4):245-246.
9. Haagsman HP. Interactions of surfactant protein A with pathogens. *Biochimica et biophysica acta*. 1998;1408(2-3):264-277.
 10. Sarno L, Della Corte L, Saccone G, et al. Histological chorioamnionitis and risk of pulmonary complications in preterm births: a systematic review and Meta-analysis. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2021;34(22):3803-3812.
 11. Choi CW, Kim BI, Kim HS, Park JD, Choi JH, Son DW. Increase of interleukin-6 in tracheal aspirate at birth: a predictor of subsequent bronchopulmonary dysplasia in preterm infants. *Acta paediatrica* (Oslo, Norway : 1992). 2006;95(1):38-43.
 12. Chaoui R, Kalache K, Tennstedt C, Lenz F, Vogel M. Pulmonary arterial Doppler velocimetry in fetuses with lung hypoplasia. *European journal of obstetrics, gynecology, and reproductive biology*. 1999;84(2):179-185.
 13. Laudy JA, de Ridder MA, Wladimiroff JW. Human fetal pulmonary artery velocimetry: repeatability and normal values with emphasis on middle and distal pulmonary vessels. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2000;15(6):479-486.
 14. Azpurua H, Norwitz ER, Campbell KH, et al. Acceleration/ejection time ratio in the fetal pulmonary artery predicts fetal lung maturity. *American journal of obstetrics and gynecology*. 2010;203(1):40.e41-48.
 15. Kim SM, Park JS, Norwitz ER, et al. Acceleration time-to-ejection time ratio in fetal pulmonary artery predicts the development of neonatal respiratory distress syndrome: a prospective cohort study. *American journal of perinatology*. 2013;30(10):805-812.
 16. Guan Y, Li S, Luo G, et al. The role of doppler waveforms in the fetal main pulmonary artery in the prediction of neonatal respiratory distress syndrome. *Journal of clinical ultrasound : JCU*. 2015;43(6):375-383.
 17. Laban M, Mansour GM, El-Kotb A, Hassanin A, Laban Z, Saleh A. Combined measurement of fetal lung volume and pulmonary artery resistance index is more accurate for prediction of neonatal respiratory distress syndrome in preterm fetuses: a pilot study. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2019;32(4):626-632.
 18. Büke B, Destegül E, Akkaya H, Şimşek D, Kazandi M. Prediction of neonatal respiratory distress syndrome via pulmonary artery Doppler examination. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2019;32(10):1640-1645.
 19. Duncan JR, Tobiasz AM, Dorsett KM, et al. Fetal pulmonary artery acceleration/ejection time prognostic accuracy for respiratory complications in preterm prelabor rupture of membranes. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2020;33(12):2054-2058.
 20. Schenone MH, Samson JE, Jenkins L, Suhag A, Mari G. Predicting fetal lung maturity using the fetal pulmonary artery Doppler wave acceleration/ejection time ratio. *Fetal diagnosis and therapy*. 2014;36(3):208-214.
 21. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*. 2007;39(2):175-191.
 22. Chaoui R, Taddei F, Rizzo G, Bast C, Lenz F, Bollmann R. Doppler echocardiography of the main stems of the pulmonary arteries in the normal human fetus. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 1998;11(3):173-179.
 23. Nowak C, Joubert M, Jossic F, et al. Perinatal prognosis of pregnancies complicated by placental chronic villitis or intervillitis of unknown etiology and combined lesions: About a series of 178 cases. *Placenta*. 2016;44:104-108.
 24. Kim CJ, Romero R, Chaemsaihong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *American journal of obstet-*

- rics and gynecology. 2015;213(4 Suppl):S53-69.
25. Oluklu D, Yildirim M, Menekse Beser D, et al. Effect of maternal autoimmune diseases on fetal pulmonary artery Doppler indices: A case-control study. *Echocardiography (Mount Kisco, N.Y.)*. 2023.
26. Turgut E, Ayhan SG, Oluklu D, Tokalioglu EO, Tekin OM, Sahin D. Fetal pulmonary artery Doppler evaluation in pregnant women after recovery from COVID-19. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2021;155(3):450-454.
27. Sule GA, Aysegul A, Selcan S, et al. Effects of SARS-COV-2 infection on fetal pulmonary artery Doppler parameters. *Echocardiography (Mount Kisco, N.Y.)*. 2021;38(8):1314-1318.
28. Oluklu D, Kara O, Turgut E, Goncu Ayhan S, Yildirim M, Sahin D. Evaluation of fetal cardiac morphology and functions in pregnant women with familial Mediterranean fever. *Echocardiography (Mount Kisco, N.Y.)*. 2022;39(4):606-611.
29. Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation*. 1983;68(2):302-309.